IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of	:	LIDDLE, John
Filing No.	:	10/561,498
Filing Date	:	December 19, 2005
Title	:	*Substituted Diketopiperazines as Oxytocin Antagonists*
Group / Art Unit	:	1612
Examiner	:	QAZI, Sabiha Naim
Confirmation No.	:	6334
Docket No.	:	PB60330

MAIL STOP APPEAL BRIEF – PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Applicants hereby appeal the Final Rejection dated December 10, 2009. This Appeal Brief is in furtherance of the Notice of Appeal filed on April 8, 2010 and is filed together with the fee under 37 CFR §41.20(b)(2). It is respectfully submitted that the instant Appeal Brief is in compliance with 37 CFR §41.37(c).

I. REAL PARTY IN INTEREST

The real party in interest is Glaxo Group Limited.

II. RELATED APPEALS AND INTERFERENCES

Appellant is unaware of any appeals, interferences, or judicial proceedings that will directly affect or be directly affected by or have a bearing on the Board's decision in the present Appeal.

III. STATUS OF CLAIMS

Claims 1-4, 7, and 9-11 are currently pending in the application. An Amendment after Notice of Appeal under 37 CFR § 41.33 is submitted concurrently with this Appeal Brief. Claims 1-3, 7, 9, and 11 are cancelled in this Amendment. Claims 4 and 10 will be pending following entry of this amendment. Claims 4 and 10 have been finally rejected and are the subject of this appeal. No claims have been substantively allowed. All of the currently-pending claims on appeal are provided in the attached appendix.

IV. STATUS OF AMENDMENTS

An Amendment After Notice of Appeal is filed concurrently with the present Appeal Brief. The Amendment cancels claims 1-3, 7, 9, and 11 and amends the dependency of claim 4 to depend from claim 10 rather than claim 1. Thus, the Amendment is in compliance with 37 CFR § 41.33.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Two claims, claims 4 and 10, will be pending in the present application following entry of the accompanying Amendment under 37 CFR § 41.33. Independent claim 10 is directed to a single stereospecific compound, (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-l,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazinedione. This claim is supported by claim 2 as originally filed. See also Example 1 on line 17 of page 12 through line 8 of page 13 of the specification. This compound is a selective antagonist of the oxytocin receptor and is useful in the treatment of oxytocin-mediated disorders. See, for example, lines 3-15 of page 3 of the specification. This compound is currently in clinical development for the treatment of pre-term labour.

Following entry of the concurrently-submitted Amendment under 37 CFR § 41.33, dependent claim 4 will be directed to a pharmaceutical composition containing a compound of claim 10.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 4 and 10 were properly rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 7,514,437.

VII. ARGUMENT

In the final Office Action, the Examiner states that claims 1-4, 7, and 9-11 are *prima facie* obvious over claims 1-12 of U.S. Patent No. 7,514,437 ('437) on the grounds that the compounds recited in the claims of the present application fall within the scope of claims 1-12 of '437. Claims 1-3, 7, 9, and 11 are cancelled in the concurrently-submitted Amendment under 37 CFR § 41.33, rendering the rejection of these claims moot. With respect to claims 4 and 10, it is noted that the recited compound does not fall within the scope of claims 5, 7, 8, or 10 of the '437 patent. Furthermore, a *prima facie* case of non-statutory obviousness-type double patenting cannot be established merely by demonstrating that the claims of a pending patent application fall within the scope of the claims of a commonly-owned patent. The Manual of Patent Examining Procedure (MPEP) states:

> Domination and double patenting should not be confused. They are two separate issues. One patent or application "dominates" a second patent or application when the first patent or application has a broad or generic claim which fully encompasses or reads on an invention defined in a narrower or more specific claim in another patent or application. Domination by itself, i.e., in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection.

MPEP § 804, citing In re Kaplan, 789 F.2d 1574, 1577-78, 229 USPQ 678, 681 (Fed. Cir. 1986); and In re Sarrett, 327 F.2d 1005, 1014-15, 140 USPQ 474, 482 (CCPA 1964). Thus, while it is true that claims 1-4, 6, 9, 11, and 12 of U.S. Patent No. '437 dominate claims 4 and 10 of the present patent application, this alone is insufficient to support a non-statutory double patenting rejection.

In the Final Office Action, the Examiner further states that "[t]he instant claimed compounds would have been obvious because one of skill in the art would have been motivated to prepare compounds embraced by the genus of the above cited references with the expectation of obtaining beneficial compounds." Office Action dated December 10, 2009, page 5, para. 2. However, the Office Action does not provide any reasoning or rationale to support the statement that the claims of the '437 patent, which encompass thousands of compounds, would direct one of ordinary skill in the art to make the specific compound claimed in the present application.

According to the Supreme Court, in order to establish a *prima facie* case of obviousness, it must be shown that there is "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). With respect to chemical compounds, the Federal Circuit has held that "[o]bviousness based on structural similarity . . . can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound." *Eisai Co. Ltd. v. Dr. Reddy's Labs, Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008), citing *Takeda Chem. Indus. V. Alphapharm Pty., Ltd.* 492 F.3d 1350, 1356 (Fed. Cir. 2007). Furthermore, "there must be some reason for starting with that lead compound other than the mere fact it exists." *Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.* 566 F.3d 999, 1007 (Fed. Cir. 2009). "[T]he attribution of a compound as a lead compound after the fact must avoid hindsight bias; It must look at the state of the art at the time the invention was made to find a motivation to select and then modify a lead compound to arrive at the claimed invention." *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.,* Fed. Cir., No. 2009-1511, 9/9/10.

In the present case, the Examiner argues "[o]ne of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference [patent] since such compounds would have been suggested by the reference as a whole." Final Office Action dated December 10, 2009, page 5, para. 3. Further, "the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious to one skilled in the art." *Id*., para. 4. However, the claims of the '437 patent encompass a genus of thousands of compounds, and the Examiner has not articulated any reason that one of skill in the art would have been motivated to (1) select any one particular compound from the many compounds recited by the claims of this patent and then (2) modify this compound in a particular way to produce a compound having the specific combination of substituents recited in claims 4 and 10 of the present application. As no such reason has been identified, a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

Finally, the Examiner states "[I]t has been decided by Courts that the indiscriminate selection of 'some' among the 'many' is considered prima facie obvious." Office Action dated December 10, 2009, page 5, para. 1. However, this statement is not relevant to the

patentability of the claims of the present application, because the compound recited in the present claims was not selected indiscriminately from amongst the genus of compounds recited in the claims of the '437 patent. In fact, the compound recited in claims 4 and 10 was selected based on its advantageous pharmacokinetic profile. Specifically, (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-l,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazinedione shows significantly improved exposure in comparison with Exemplary compound 180 of the '437 patent. See Table 4 of Liddle et al. (2008) Bioorg. Med. Chem. Lett.18(1):90-4 (attached herewith as **Appendix A**), which shows the area under the plasma concentration time curve (AUC) for compound of Example 180 of the '437 patent (labeled as compound **20**) in comparison with that of (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-l,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazinedione (labeled as compound **22**). Liddle *et al.* further state:

> **22**, GSK21149A, had greater oral exposure in the rat compared to 20 in both DMSO/Peg and HPMC/Tween formulations, with good bioavailability and a half life of 1.4h h. Compound **22** also has low to moderate intrinsic clearance in microsomes from three pre-clinical species (rat, dog, cynomolgus monkey) and low intrinsic clearance in human microsomes and is more potent than 20. Although several amide analogues of **22** were prepared, with a range of physiochemical properties, **22** offered the preferred overall profile . . . [w]ith this data in hand, **22**, GSK221149A, was selected for progression to further selectivity and in vivo efficacy models. GSK22149A is a potent and selective oxytocin receptor antagonist (Table 5) with no detectable agonist activity.

Liddle *et al.*, page 92, column 2, paras. 2-3.

The claims of the '437 patent provide no suggestion that the stereospecific compound as recited in claims 4 and 10 would have the advantageous pharmacokinetic profile described in the Liddle *et al.* reference. Accordingly, even if the Examiner had established a *prima facie* case of non-statutory obviousness-type double patenting, the Applicant has submitted sufficient evidence to rebut such a case.

In conclusion, the Final Office Action fails to provide all the elements required for a *prima facie* showing of non-statutory obviousness-type double patenting because the Examiner has not identified a reason why a person of ordinary skill in the art would combine the elements recited in claims 1-12 of U.S. Patent No. 7,514,437 to produce the compound claimed in claims 4 and 10 of the present application.

CONCLUSION

Accordingly, the Board is respectfully requested to reverse the final rejections and remand this application for issuance.

Respectfully submitted,

/Kathryn L. Coulter/

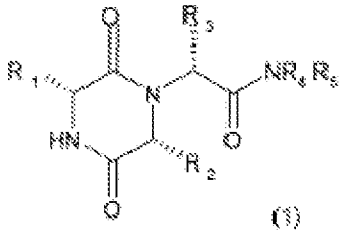
Kathryn L. Coulter
Attorney for Applicants
Reg. No. 45,889

Date: 09/13/2010

Customer No. 23347
GlaxoSmithKline
Global Patents
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709-3398
Telephone: (919) 483-1467
Facsimile: (919) 483-7988

VIII. CLAIMS APPENDIX

1. A compound of formula (1)



(I)

wherein R_1 is 2-indanyl, R_2 is 1-methylpropyl, R_3 is 2-methyl-l,3-oxazol-4-yl and R_4 and R_5 together with the nitrogen atom to which they are attached represents morpholino, or a pharmaceutically acceptable salt thereof.

2. A compound which is (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazinedione, or a pharmaceutically acceptable salt thereof.

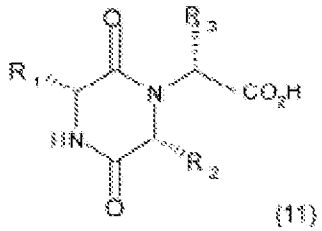
3. A compound which is (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1R)-1-methylpropyl]-2,5-piperazinedione, or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound of formula (1) as claimed in 1 together with one or more pharmaceutically acceptable carriers.

5 – 6. (Cancelled)

7. A process for the preparation of compounds of formula (I) which comprises:

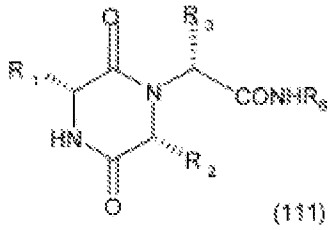
(a) reacting a compound of formula (II)



(II)

wherein R_1, R_2 and R_3 have the meanings defined in claim 1 or a mixed anhydride thereof, with the amine NHR_4R_5 wherein R_4 and R_5 have the meaning defined in formula (I) under the standard condition for preparing amides from a carboxylic acid or a mixed anhydride thereof and an amine; or

(b) reacting a compound of formula (III)



(111)

wherein R_1, R_2 and R_3 have the meanings defined in claim 1 and R_6 is 2-hydroxyphenyl with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent and subsequent reaction of the product thus formed with amine NHR_4R_5 wherein R_4 and R_5 have the meaning defined in formula (I).

8. (Cancelled)

9. A pharmaceutical composition of claim 4, wherein the compound is (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazinedione.

10. A compound which is (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-l,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-1-methylpropyl]-2,5-piperazinedione.

11. A pharmaceutically acceptable salt of (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-(4-morpholinyl)-2-oxoethyl]-6-[(1S)-l-methylpropyl]-2,5-piperazinedione.

IX. EVIDENCE APPENDIX

Reference attached as APPENDIX A:

LIDDLE *et al*., "The Discovery of GSK221149A: A Potent and Selective Oxytocin Antagonist," *Bioorganic & Medicinal Chemistry Letters*, 2008, Vol. 18, pp. 90-94.

X. RELATED PROCEEDINGS APPENDIX

None.

APPENDIX A

Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 18 (2008) 90–94
Bioorganic & Medicinal Chemistry Letters

The discovery of GSK221149A: A potent and selective oxytocin antagonist

John Liddle,[a,*] Michael J. Allen,[d] Alan D. Borthwick,[a] David P. Brooks,[c] David E. Davies,[a] Richard M. Edwards,[c] Anne M. Exall,[a] Chris Hamlett,[a] Wendy R. Irving,[a] Andrew M. Mason,[a] Gerald P. McCafferty,[c] Fabrizio Nerozzi,[a] Simon Peace,[a] Joanne Philp,[a] Derek Pollard,[a] Mark A. Pullen,[c] Shaila S. Shabbir,[b] Steve L. Sollis,[a] Timothy D. Westfall,[c] Pat M. Woollard,[b] Charlene Wu[c] and Deirdre M. B. Hickey[a]

[a]*Department of Medicinal Chemistry, GlaxoSmithKline Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK*
[b]*Department of Drug Metabolism and Pharmacokinetics, GlaxoSmithKline Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK*
[c]*Department of Urogenital Biology, Cardiovascular and Urogenital Centre of Excellence for Drug Discovery, GlaxoSmithKline Research and Development, King of Prussia, PA, USA*
[d]*Department of Molecular Discovery Research, GlaxoSmithKline Research and Development, New Frontiers Science Park, Harlow, Essex, UK*

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Abstract—Optimisation of a series of oxazole diketopiperazines has led to the discovery of a very potent and selective oxytocin antagonist GSK221149A. GSK221149A has been shown to inhibit oxytocin-induced uterine contractions in the anaesthetised rat.

Preterm labour occurs in 10% of all births worldwide and is the single largest cause of neonatal morbidity and death.[1] Although it is difficult to estimate the cost of neonatal intensive care of low birth-weight babies, it is thought to exceed $5 billion/year in the US alone.[2] Oxytocin (OT), a cyclic nonapeptide neurohypophyseal hormone, binds to OT receptors stimulating contractility in human myometrium and is widely used for the induction of labour.[3] The density of oxytocin receptors in myometrium is elevated during pregnancy and it is believed that a premature increase of such receptors can initiate preterm labour by sensitising the uterus to relatively unchanged circulating levels of OT.[4,5] The design of OT antagonists as potential tocolytic agents for the prevention of premature labour has therefore been an intense area of research for many years.[6] Although the peptide OT antagonist atosiban has been approved for clinical use in Europe, it is not orally bioavailable and has low plasma stability rendering it less likely to be useful for long-term or preventative treatment.[7] Atosiban also has a greater affinity for the vasopressin V_{1a} receptor than the oxytocin receptor.[8]

We recently reported the diketopiperazine **1** to be a potent and orally bioavailable OT antagonist (Table 1).[9] Compounds of this series had been hindered by poor physicochemical properties, including low solubility and relatively high log *D*, which consequently led to relatively high plasma protein binding and cytochrome P450 interactions, with high clearance in cynomolgus monkey and human microsomes.

Structure–activity relationships (SAR) had indicated that both the indanyl and isobutyl fragments contributed to potency,[13] and hence we sought to investigate the modification of the exocyclic aryl and amide functionality. Herein, we describe our efforts around the five-membered ring heterocycles to improve the poor

Keywords: Oxytocin; Labour; Diketopiperazine; Tocolytic.
* Corresponding author. E-mail: john.2.liddle@gsk.com

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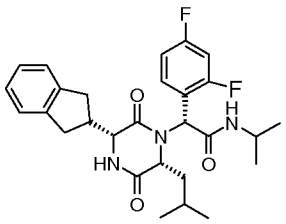
doi:10.1016/j.bmcl.2007.11.008

Table 1. Physicochemical properties of **1**



hOT pK_i[10]	8.9–9.2
Log$D$[a]	3.4
HSA[b]	93%
Sol.	<1 μg/mL
CYP450 3A4 IC_{50}	4 μM

1

[a] Chromatographic lipophilicity measurement.[11]
[b] Human serum albumin binding.[12]

physicochemical and pharmacokinetic properties of this series.

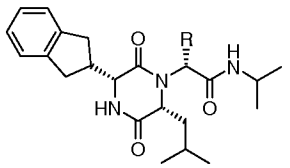
Replacing the difluorophenyl ring with unsubstituted five-membered ring heterocycles resulted in approximately a 10-fold loss in intrinsic potency (Table 2). Potency was regained on the introduction of a lipophilic group, such as methyl or bromide, in the 4 or 5 position. In an attempt to access the putative lipophilic pocket reached by these substituents, a number of trifluoromethyl heteroaryls were prepared. The CF_3 group was invariably the most potent substituent but its strongly electron withdrawing nature led to epimerisation of the exocyclic position in neutral or mildly basic media rendering the compounds less attractive for developability reasons.

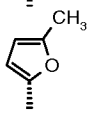
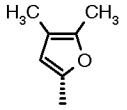
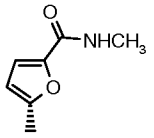
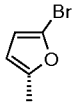
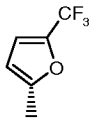
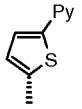
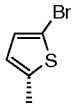
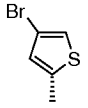
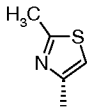
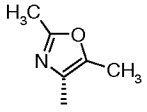
Polar groups were poorly tolerated; the methylamide **6** was significantly less potent than the parent furan 3 although large substituents, such as phenyl and pyridyl (analogue 9), were tolerated. Disubstitution in both the 4 and 5 positions did not increase potency further. Methyl substitution ortho to the ring junction was tolerated as exemplified by the dimethyl oxazole **14** having similar potency to the methyl oxazole **15**. Although the SAR trends were consistent across all heterocycles, the absolute potencies were often significantly different. The difference in potencies of similarly substituted heterocycles may therefore be a reflection of the heterocycle's ability to orientate the substituent into a lipophilic pocket of the receptor.

Although the introduction of lipophilic substituents gave favourable binding affinities, unsurprisingly this was generally accompanied by poor physicochemical properties (Table 3). Indeed, the furyl and thiophene derivatives were poorly water-soluble, relatively highly protein bound and carried undesirable CYP450 interactions (results for the 3A4 isozyme are shown in Table 3). More polar azoles were able to accommodate lipophilic substituents whilst maintaining good physicochemical properties. The oxazole analogues had good aqueous solubility, low protein binding and minimal CYP450 interaction making the series most attractive for further investigation.

Established SAR suggested that a range of amides was tolerated and we therefore envisioned using this functionality as a handle to optimise the pharmacokinetic profile. Potency and pharmacokinetic data on selected

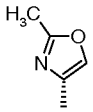
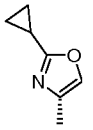
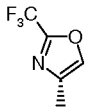
Table 2. Inhibition of the binding of OT at the human OT receptor[10]



Compound	R	hOT pK_i
2[a]		7.9
3		8.2
4		9.0
5		8.9
6		7.4
7		9.1
8		10.0
9[c]		8.6
10		8.7
11		9.0
12		8.2
13[b]		9.4
14[b]		8.5

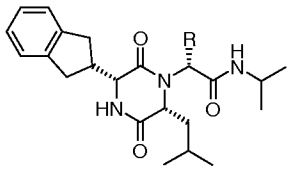
(*continued on next page*)

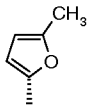
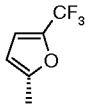
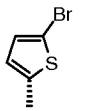
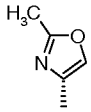
Table 2 (*continued*)

Compound	R	hOT pK_i
15		8.9
16[b]		9.1
17		9.8

[a] *tert*-Butyl amide rather than isopropylamide.[14]
[b] Dimethylamide rather than isopropylamide.[14]
[c] Py, 2-pyridyl.

Table 3. Properties of selected compounds



Compound	R	hOT pK_i	Log D[a]	HSA[b]	CYP450 3A4 IC_{50}[c]	Sol. (μg/ml)
4		9.0	3.3	96	7	34
8		10.0	3.6	97	3	<1
10		8.7	3.7	99	1	<1
15		8.9	2.5	63	>100	>240

[a] Chromatographic lipophilicity measurement.[11]
[b] Human serum albumin binding (%).[12]
[c] Lowest IC_{50} from CYP450 3A4 using substrates diethoxyfluoroscein (DEF), 7-{3-(4-phenylpiperazin-1-ylmethyl)benzyl}resorufin (PPR) or 7-benzyloxyquinoline (7-BQ).

amides are recorded in Table 4. The oxazole amides **18**–**22** had good aqueous solubility (>220 μg/mL), low plasma protein binding (<80% HSA) and no significant cytochrome P450 interactions (CYP3A4 IC_{50} > 100 μM). As expected, a range of functionality could be incorporated in the amide without having detrimental effects on potency. Compounds **15** and **18**–**22** demonstrated antagonist activity in an in vitro functional assay and were selective with respect to the vasopressin V_{1a} receptor (>10-fold). Oxazoles with polar amide substituents, such as the alcohol **18**, had poor oral exposure in the rat. Good pharmacokinetic profiles were achieved with less-polar amides. Tertiary amides **19** and **20** had moderate clearances and volumes of distribution of approximately 1 L/kg resulting in half lives of around 1 h. Both compounds had acceptable bioavailabilities in rat in excess of 30%.

The SAR of the isobutyl portion of **1** was sensitive to relatively minor modifications (Table 4) which had dramatic effects on the pharmacokinetic profile. Branching at the α-carbon was tolerated and resulted in a superior rat pharmacokinetic profile.

Indeed **22**, GSK221149A, had greater oral exposure in the rat compared to **20** in both DMSO/Peg and HPMC/Tween formulations, with good bioavailability and a half life of 1.4 h. Compound **22** also has low to moderate intrinsic clearance in microsomes from three pre-clinical species (rat, dog, cynomolgus monkey) and low intrinsic clearance in human microsomes and is more potent than **20**. Although several amide analogues of **22** were prepared, with a range of physicochemical properties, **22** offered the preferred overall profile.

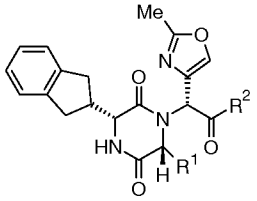
With this data in hand, **22**, GSK221149A, was selected for progression to further selectivity and in vivo efficacy models. GSK221149A is a potent and selective oxytocin receptor antagonist (Table 5) with no detectable agonist activity. GSK221149A is greater than 10-fold more potent than atosiban with a far superior selectivity profile with respect to vasopressin receptors.[15]

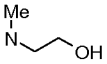
The in vivo activity of GSK221149A was evaluated in anaesthetised, non-pregnant Sprague–Dawley female rats.[15] Uterine activity was measured as an integral of force over time. Intravenous administration of GSK221149A produced a dose-dependent decrease in oxytocin-induced uterine contractions, with an $ID_{50} = 0.27 \pm 0.60$ mg/kg and IC_{50} = 180 nM.

The synthesis of the diketopiperazines followed previously described chemistry.[16] The isopropyl amides were conveniently prepared in three steps from the corresponding isonitrile via the Ugi reaction as outlined in Scheme 1. The intermediate mixture of diastereoisomers **23** was deprotected with 4 M HCl and subsequently cyclised by treatment with base in a one-pot procedure. Generally, a 2:1 mixture of diastereoisomers was formed with the desirable (*R*)-isomer **8** being the minor product isolable by chromatography.

GSK221149A and other tertiary amides were prepared in four steps via the Ugi reaction as outlined in Scheme 2. A 2:1 mixture of diastereoisomers **24** was formed with the desirable (*R*)-diastereoisomer being the minor product. Hydrogenation of crude **24** furnished the cyclised phenol **25**, again enriched with the undesirable (*S*)-diastereoisomer. Activation of the mixture **25** with carbonyl diimidazole followed by the addition of 2 N HCl promoted epimerisation at the exocyclic position

Table 4. Profile of selected oxazoles



Compound	R^1	R^2	hOT pK_i	Rat PK (iv 2 mg/kg, po 5 mg/kg)			
				Cl[a]	$t_{1/2}$[b]	AUC[c]	F[d] (%)
15		NH*i*-Pr	8.9			225[e]	
18			8.9			218[e]	
19			8.8	35	1.4	1070[e]	45
20			8.7	23	1.1	3633[e] 1190[f]	33
21			8.2	14	1.3	4200[e]	69
22			9.0	19	1.4	5470[e] 1800[f]	~100 42

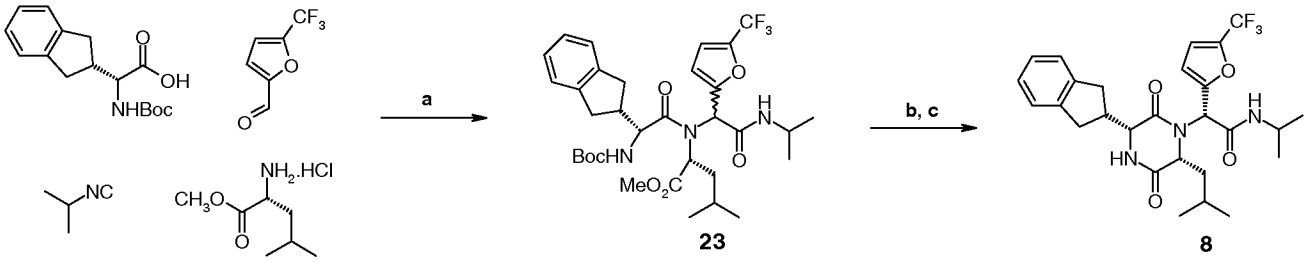
IV formulation 5:95 20% polyvinylpyrrolidone in DMSO: 35% sulfobutylether-7-betacyclodextrin in water.
[a] Clearance (mL/min/kg).
[b] Half life (h).
[c] AUC (hr ng/ml).
[d] Bioavailability.
[e] PO formulation 5:95 DMSO/PEG400 using amorphous.
[f] PO formulation: hydroxypropylmethylcellulose (HPMC)/Tween using crystalline material.

Table 5. Binding affinity at recombinant/native receptors

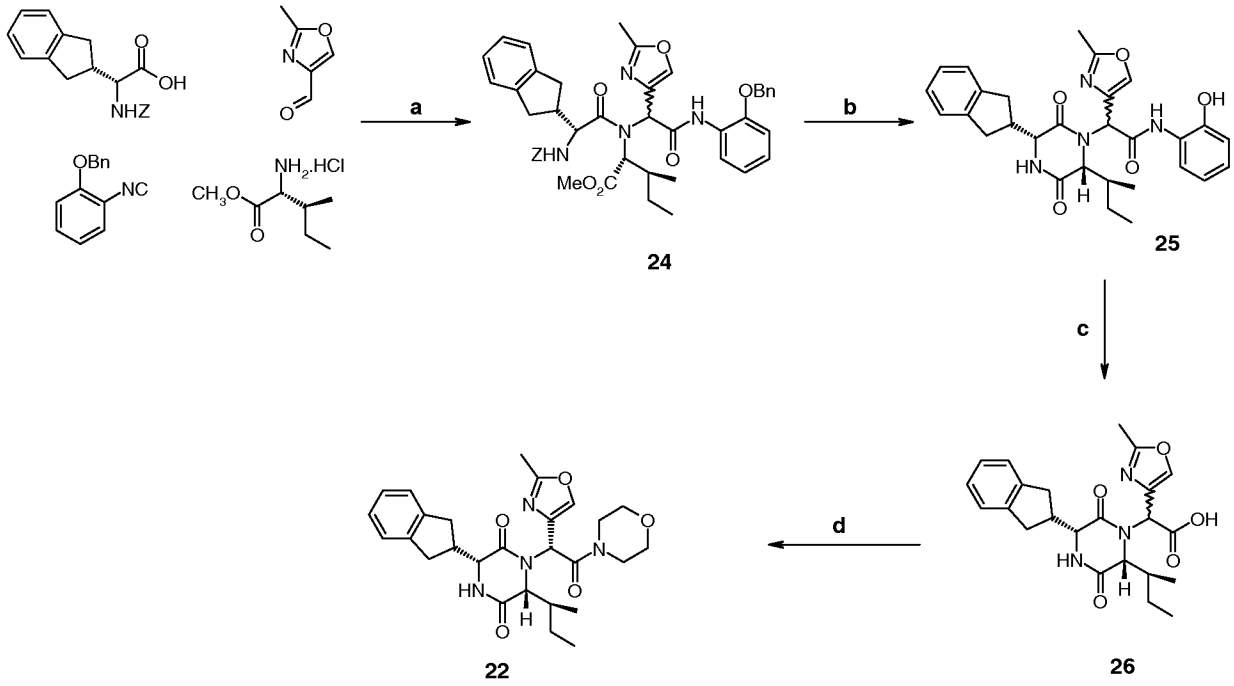
Receptor	GSK221149A K_i (nM)	Atosiban K_i (nM)
hOT	0.65	11
rOT	4.1	32
hV_{1a}	>12,000	0.15
hV_{1b}	>10,000	44
hV_2	950	330

and yielded the acids **26** with the required (*R*)-diastereoisomer as the major product. Acid activation with benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate followed by the addition of morpholine and subsequent column chromatography yielded homochiral GSK221149A.

In conclusion, GSK221149 has nanomolar affinity for the oxytocin receptor with >1400-fold selectivity over the closely related vasopressin receptors. GSK221149A has a good rat pharmacokinetic profile, low human microsomal clearance and has been shown to inhibit oxytocin-induced contraction in vivo in the anaesthetised rat.



Scheme 1. Reagents: (a) triethylamine, MeOH; (b) 4 M HCl in dioxan, MeOH; (c) triethylamine, DCM.



Scheme 2. Reagents and conditions: (a) triethylamine, MeOH; (b) H_2, Pd/C, ethanol/acetic acid; (c) carbonyl diimidazole, CH_2Cl_2 3 h then acetone/2 N HCl; (d) benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, dichloromethane 1 h then morpholine.

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